
Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors.

Journal: Cancer Cell

Publication Year: 2008

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PubMed link: 18394555

Funding Grants: Derivation and Characterization of Cancer Stem Cells from Human ES Cells, Interdisciplinary Stem Cell Training Program at UCSD

Public Summary:

Scientific Abstract:

Polycythemia Vera (PV) is a myeloproliferative disorder (MPD) that is commonly characterized by mutant JAK2 (JAK2V617F) signaling, erythrocyte overproduction, and a propensity for thrombosis, progression to myelofibrosis, or acute leukemia. In this study, JAK2V617F expression by human hematopoietic progenitors promoted erythroid colony formation and erythroid engraftment in a bioluminescent xenogeneic immunocompromised mouse transplantation model. A selective JAK2 inhibitor, TG101348 (300 nM), significantly inhibited JAK2V617F+ progenitor-derived colony formation as well as engraftment (120 mg/kg) in xenogeneic transplantation studies. TG101348 treatment decreased GATA-1 expression, which is associated with erythroid-skewing of JAK2V617F+ progenitor differentiation, and inhibited STAT5 as well as GATA S310 phosphorylation. Thus, TG101348 may be an effective inhibitor of JAK2V617F+ MPDs in clinical trials.

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